REMARKS

Reconsideration and withdrawal of the rejections of this application are respectfully requested.

I. Status of Claims and Formal Matters

Claims 1, 7-9, 14, 15 and 19-29 are under examination in this application. Claims 1, 15 and 27 are amended herein to more clearly define the claimed subject matter. Claims 23-26 are now cancelled.

No new matter has been added by the amendments. Support for the amendments and new claims is found throughout the application as originally-filed and from the pending and original claims.

Claims 1 and 27 are amended herein to specify that the topical excipient effectively delivers the ketamine and morphine to local peripheral receptors and not to central receptors Exemplary support for the amendments is provided on page 9, lines 28-35 of the specification, where therapeutically effective delivery of active agents of the invention to peripheral receptors but not central receptors is described. Further support is provided on page 20, lines 1-10 and lines 23-25 of the specification, as discussed in detail herein below.

It is submitted that the claims, herewith and as originally presented, are patentably distinct over the prior art cited by the Examiner, and that these claims were in full compliance with the requirements of 35 U.S.C. § 112. The amendment of the claims, as presented herein, is not made for purposes of patentability within the meaning of 35 U.S.C. §§ 101, 102, 103 or 112. Rather, this amendment is made simply for clarification and to round out the scope of protection to which Applicants are entitled. Furthermore, it is explicitly stated that the herewith amendment should not give rise to any estoppel.

Reconsideration and withdrawal of the objections to and the rejections of this application in view of the amendments and remarks herewith, is respectfully requested, as the application is in condition for allowance.

II. The Rejections Under 35 U.S.C. § 112 Are Overcome

Claims 1, 7-9, 14, 15 and 19-29 are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. Applicants respectfully disagree and traverse this rejection.

Independent claims 1, 9, 15 and 27 claim pharmaceutical compositions or methods of providing analgesia that exclude effective systemic delivery of the active agents to the central nervous system. These limitations specify that the active agents of the invention (i.e., morphine and ketamine) are effectively delivered or function through local receptors in the periphery and not through central receptors of the central nervous system. The rejection of June 29, 2005 has been maintained, and alleges that "the claims contain subject matter that is not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention."

Applicants reiterate their position as stated in the response filed on September 29, 2005 and April 18, 2006 with respect to this rejection. A comprehensive reading of the specification easily conveys to one skilled in the art that the exclusion of systemic effects mediated by central receptors was a well described embodiment of the invention. For example, one skilled in the art reading the passage on page 9, lines 28-35 (where it is stated that the topical formulations of the invention are not required to deliver the active ingredients to the central receptors), would instantly recognize that the alternative embodiments of the invention where central delivery was not required were intended to exclude effective delivery from the central receptors. This passage states:

> A topical formulation of the present invention delivers a therapeutic effect on the peripheral opiate receptors and is not required to deliver the active ingredients in the topical formulation to central (brain and spinal cord) opiate receptors. The topical formulations of the present invention provides local delivery of the active ingredients and is not required to provide systemic delivery of the active ingredients in the formulation in the treated mammals.

As another example, page 15, lines 13-19 discourages the administration of ketamine to central receptors. This passage states:

> Except for dextromethorphan, many current NMDA receptor agonists have not been suitable for systemic clinical use due to profound psychomimetic effects. Such NMDA receptor antagonists, however, may be used in the present invention in topical formulations.

Here, the specification makes clear that ketamine, which is the NMDA receptor agonist, would not be delivered to central receptors in effective amounts, as such delivery can have adverse effects.

Importantly, this embodiment of the invention has been exemplified. Examples 2-7 describe topical administration of an opioid, such as morphine or M6G, to the tails of mice. Examples 6-7 describe topical administration of an NMDA receptor antagonist, such as MK801 or ketamine, to the tails of mice. The effect of this topical administration paradigm was localized to the peripheral receptors and excluded effective delivery to central receptors, as stated on page 20, lines 1-10 and lines 23-25:

> The tail immersion technique has a number of advantages. Foremost is the ability to repeatedly treat the mice without tissue damage secondary to injections. The paradigm was selective for local mechanisms. Testing proximal regions of the tail failed to reveal any analgesic response, confirming the distribution studies with ^{125}I-opioid which documented the localization of the radiolabel only to the regions immersed in drug solution and the absence of any detectable uptake into the blood or the central nervous system. ... In all cases, proximal segments of the tail which were not exposed to the opioid solution were not analgesic, confirming the peripheral site of action for the sites immersed in the opioid solution.

Thus, effective delivery of the active agents "to local peripheral receptors and not to central receptors" is extensively described in the instant specification.

Despite the Applicant's strong showing of support for claim language that would exclude effective systemic delivery of the active agents to central receptors, it is stated in the Advisory

Action of May 5, 2006 that the application provides no support for such limitation and further, that the exemplified results discussed above provide support only for "a specific mammal (rat) in a specific skin area (tail)."

It is believed that a review of the proper legal standard under 35 USC § 112, first paragraph, would be helpful in assessing the burden that is on the Office in challenging an Applicant's written description. A description as filed is presumed to be adequate, unless or until sufficient evidence or reasoning to the contrary has been presented by the Examiner to rebut the presumption. See, e.g., *In re Marzocchi*, 439 F.2d 220, 224, (C.C.P.A. 1971). The Examiner, therefore, must have a reasonable basis to challenge the adequacy of the written description. The Examiner has the initial burden of presenting by a preponderance of evidence why a person skilled in the art would not recognize in an applicant's disclosure a description of the invention defined by the claims. *In re Wertheim*, 541 F.2d 257, 263 (C.C.P.A. 1976). *See* M.P.E.P. 2163.04.

It is respectfully submitted that the rationale put forth in the instant Office Action to establish that the skilled artisan would not find the claimed invention in the instant specification is not a reasonable basis for challenge under § 112 and does not amount to a preponderance of the evidence. The entire basis for the instant challenge under § 112 is apparently limited to a finding that the arguments above are "unconvincing" because the description at page 15, lines 13-19 teaches only that systemic delivery is undesirable due to psychomimetic effects and that the description at page 20, lines 1-10 and 23-25 would only convey an expected result in the tail of a rat.

The teaching in the specification must be taken as a whole. The disclosure at page 9, lines 28-35 of the specification teaches that a restricted effect in the periphery is within the ambit of the invention, the disclosure at page 15, lines 13-19 of the specification describes an advantage associated with the restricted effect and page 20, lines 1-10 and lines 23-25 of the specification provide a detailed account of the restricted effect within a mammal. The instant rejection is not supported by reasonable and preponderant evidence to the contrary, as is required by M.P.E.P. 2163.04.

Furthermore, to comply with the written description requirement of 35 U.S.C. § 112, each claim limitation must be expressly, implicitly, or inherently supported in the originally filed disclosure. *See* M.P.E.P. 2163.05. Even if the claimed invention is not expressly disclosed—and

it is believed that it is—the written description requirement is satisfied by the implicit disclosure, for example, at page 9, lines 28-35. Moreover, simply rephrasing a passage does not constitute new matter. *In re Anderson*, 471 F.2d 1237, (C.C.P.A. 1973) (emphasis added). At most, the language of claims 1, 9, 15, 23 and 27 rephrases the disclosure at page 9, lines 28-35, of the specification.

The allegation that the exemplified results at page 20, lines 1-10 and lines 23-25 of the specification fail to provide support for topical administration to all mammals is equally misplaced. The fundamental factual inquiry which applies is whether the specification conveys with reasonable clarity to those skilled in the art that the Applicant was in possession of the invention as now claimed. See, e.g., *Vas-Cath, Inc.*, 935 F.2d 1563-64 (Fed. Cir. 1991). The exemplification unambiguously demonstrates the ability of the claimed methods and compositions to provide analgesia exclusively to peripheral sites of action, placing the Applicant in possession of the invention at the time that the application was filed.

Finally, the declaration of Gavril W. Pasternak, Ph.D., unequivocally shows that one of ordinary skill in the art would have recognized the use of the tail-flick model of nociception and understood its predictive applicability in higher mammals, particularly humans. In particular, the tail-flick assay was accepted by those of skill in the art for its reliability in predicting clinical outcome of opioid analgesics (e.g., morphine) in other mammals, including humans.

In view of the foregoing, reconsideration and withdrawal of all rejections under 35 U.S.C. § 112 are respectfully requested.

III. The Rejections Under 35 U.S.C. § 103 Are Overcome

Claims 1, 9, 14, 15, 19-23, 26 and 27 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Yakesh (U.S. Patent No. 5,849,761; hereinafter "Yakesh") in view of Mayer *et al.* (U.S. Patent No. 5,635,204; hereinafter "Mayer"). It is alleged that the combination of Yakesh and Mayer renders obvious a topical composition comprising morphine, ketamine and an excipient. Applicants respectfully disagree and traverse the rejection. It is respectfully asserted that the combination of cited references fail to teach or suggest compositions or methods for providing morphine, ketamine and an excipient exclusively to the periphery.

Yakesh describes and claims methods of using anti-diarrheal compounds that interact with peripheral opiate receptors but that do not elicit central nervous system side effects. To

demonstrate the need for these anti-diarrheal compounds, Yakesh elaborates on the problems in the art. At column 3, lines 66-67, through column 4 lines 1-8 Yakesh states:

> Opiates, such as morphine, however, when peripherally applied, have a short duration of action and possibly can, if applied at sufficient levels, have effects upon consciousness and respiration. The possible systemic effects, CNS effects and abuse potential render conventional opioids **unsuitable for local application** and unsuitable as peripheral anti-hyperalgesics. Thus, there is a need for effective anti-hyperalgesics that directly block peripheral sensitization, but that do not have concomitant central nervous system effects, including the potential for abuse (emphasis added).

Yakesh does not teach a topical composition comprising morphine, ketamine or morphine and ketamine for exclusive use in the periphery.

Mayer teaches a drug combination comprising a first analgesic, a second component and an NMDA receptor antagonist. Mayer discloses only systemic means of administration for the drug combination. Mayer is silent regarding the significant role that peripheral sites play in the development of tolerance, and the dose-lowering effect of NMDA receptor antagonists on opioids in the periphery. Accordingly, Mayer does not teach a topical composition or method for exclusive use in the periphery, much less suggest any need therefor.

Yakesh, taken in combination with Meyer, teaches away from the use of "conventional opioids" in the periphery. Yakesh alerts one skilled in the art of providing analgesia to problems associated with the use of "conventional opioids" in the periphery and offers as a solution an alternate therapeutic regimen. Meyer does the same, by teaching that a therapeutic benefit results only from a systemic course of administration. Taken together, the combination of Yakesh with Meyer teaches away from the application of conventional opioids (e.g., morphine) to the periphery and thus, teaches away from the claimed invention.

For the §103 rejection to be proper, both the suggestion of the claimed invention and the expectation of success must be founded in the prior art, and not Applicants' disclosure. *In re Dow*, 5 U.S.P.Q.2d 1529, 1531 (Fed.Cir. 1988). There must also be some prior art teaching which would have provided the necessary incentive or motivation for modifying the reference teachings. *In re Laskowski*, 12 U.S.P.Q. 2d 1397, 1399 (Fed. Cir. 1989); *In re Obukowitz*, 27 U.S.P.Q. 2d 1063 (BOPAI 1993).

At the time the application for the present invention was filed, there was no reasonable expectation of success in practicing the claimed invention. As previously documented in the Office Action Responses dated April 11, 2005, and September 29, 2005—to which there has been no meaningful reply—several medical reports published both before and after the filing of the present application teach that in clinical applications, morphine fails to stimulate peripheral sites. *See,* for example, Moore (1994), Picard (1997) and Yarussi (1999), previously cited. These studies demonstrate that the effectiveness of tolerance attenuated doses of morphine in the periphery was unexpected given the state of the art. Nothing in Yakesh challenges or contradicts this understanding of the state of the art with respect to topical morphine.

In the present Office Action, it is alleged that the claimed invention is obvious because "Yakesh teaches that it is known in the art that the concentration of morphine must be sufficiently low to avoid systemic and CMS side effects." However, given the lack of efficacy reported for topical morphine, acknowledged even by Yakesh (reporting its short duration of action), low doses of morphine for exclusive use in the periphery would not have been the obvious choice for the skilled practitioner. Combining the teachings of Mayer with Yakesh provide no more encouragement to the skilled practitioner, as Mayer fails to teach or suggest a dose lowering effect of ketamine on morphine analgesia in the periphery, and the combination of Yakesh with Mayer only directs the skilled practitioner further away from the use of morphine in the periphery.

The requisite expectation of success must be found in the prior art, and not the Applicants' disclosure. *Id.* The combination of cited references provides no reasonable expectation of success in practicing the claimed invention. It is only the teaching in the Applicants' disclosure that shows the dose lowering effect of ketamine on morphine analgesia exclusively in the periphery, thereby enabling effective compositions and methods comprising topical morphine. At best, the proposed combination is "obvious to try," however, it has long been established that this is not the standard of 35 U.S.C. § 103. *In re Geiger*, 815 F.2d 686, 655 (Fed. Cir. 1987).

Furthermore, there is no motivation for the skilled artisan to look to the teachings of Yakesh, much less modify the teachings of the same in combination with Mayer to localize and manage morphine analgesia in the periphery. The present Office Action states that "Yakesh teaches that the formulation of morphine for only peripheral use is known in the art when

concentrations are sufficiently low." To the contrary, what Yakesh teaches is that the use of morphine in the periphery is "unsuitable for local application" due to its short duration of action and high potential for side effects. Yakesh does not teach, suggest or provide any reasonable expectation of success for topical morphine compositions in the periphery. Rather, Yakesh rejects the use of morphine in the periphery and provides clear alternatives to this course of treatment.

As stated by the Court in *In re Fritch*, 23 U.S.P.Q. 2d 1780, 1783-1784 (Fed. Cir. 1992): "The mere fact that the prior art may be modified in the manner suggested by the Examiner does not make the modification obvious unless the prior art suggests the desirability of the modification." Yakesh clearly discourages the use of conventional opioids, such as morphine, in the periphery. Mayer is silent regarding the significant role that peripheral sites play in the development of tolerance, and the dose-lowering effect of ketamine on morphine in the periphery. Thus, in the present Office Action, the art is only modified as suggested by the Examiner, as Yakesh and Mayer in combination fail to provide any indication of the desirability for making such modifications to provide morphine analgesia selectively to the periphery.

Claims 7, 8, 24, 25, 28 and 29 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Yakesh and Mayer as applied to claims 1, 9, 14, 15, 19-23, 26 and 27 and further in view of Mackles. Applicants respectfully disagree and traverse the rejection. It is respectfully asserted that the cited references fail to teach or suggest a composition or use of morphine, ketamine and lidocaine having an exclusive effect in the periphery. The combination of Yakesh and Meyer fails to teach or suggest the claimed invention as discussed in detail herein above. The further combination of Mackles with Yakesh and Meyer and fails to cure the defects associated with the combination of Yakesh and Meyer, or in any way teach or suggest the claimed invention.

Reconsideration and withdrawal of the rejections under 35 U.S.C. §103 are requested.

CONCLUSION

In view of the amendments and remarks herewith, the application is believed to be in condition for allowance. Favorable reconsideration of the application and prompt issuance of a Notice of Allowance are earnestly solicited. The undersigned looks forward to hearing favorably from the Examiner at an early date, and, the Examiner is invited to telephonically contact the undersigned to advance prosecution. The Commission is authorized to charge any fee occasioned by this paper, or credit any overpayment of such fees, to Deposit Account No. 04-1105.

Respectfully submitted,

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